REMARKS

Claims 1-3, 5-11, 18-23, 36, 44, 85-87, 89, and 96-126 constitute the pending claims in the present application.

Claim Rejections Under 35 U.S.C. §103

Claims 1-3, 5-11, 18-19, 22-23, 36, 96, 99, 100-101, 104-126 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas et al. (a) in view of Dower et al. and Barbas et al. (b) in view of Cwirla et al. and further in view of Wrighton et al. as evidenced by Helms.

Applicants respectfully submit that the references cited by the Examiner, taken alone or in any combination, fail to teach or suggest an immunoglobulin molecule, or fragment thereof, wherein an agonist peptide (such as an EPO or TPO mimetic) replaces a single portion of a complementarity determining region and wherein the immunoglobulin molecule or fragment thereof binds to and agonizes a receptor (such as an EPO or TPO receptor) as claimed in the instant application.

The Examiner appears to be rejecting the claims based on some teaching, suggestion, or motivation to combine prior art references. The guidelines with regard to this standard are set forth in Rationale G in the Examination Guidelines for Determining Obviousness under 35 U.S.C. 103 (see Federal Register, Volume 72, No. 195, pages 57526-57535 (October 10, 2007)):

G. Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention;

(1) a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings;

(2) a finding that there was reasonable expectation of success; and

(3) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

As noted in Applicants' previous responses, Barbas et al. (a) discloses inserting peptides into CDR regions to generate antagonists (see e.g., page 75, lines 29-34, and pages 78-83). Barbas (b) discloses autoantibodies that bind to DNA. Such antibodies do not even bind to a receptor let alone

suggest that such antibodies could be used to *agonize* receptor activity. Possibly the Examiner meant to cite to a different publication, this being Barbas et al., *Proc. Natl. Acad. Sci. USA* 88:7978-7982 (1991). The Examiner suggests that a person skilled in the art would have been motivated and had a reasonable expectation of success by combining the CDR replacement strategy of Barbas et al. (a) with the peptides of Cwirla and Wrighton. Applicants strenuously disagree.

"[R]ejections on obviousness cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." Examination Guidelines for Determining Obviousness under 35 U.S.C. 103, citing KSR International Co. v. Teleflex, Inc., 550 U.S. __, 127 S.Ct. 1727, 82 U.S.P.Q.2d 1385 (2007).

As noted in Applicants' response of April 19, 2007, nothing in the cited references or in the general knowledge teaches the combination of Cwirla, Wrighton, or Helms with either Barbas reference. Cwirla and Wrighton are directed to the discovery of *small peptides* that can be used as agonists of the EPO or TPO receptor. In particular, both references utilize a phage display library to isolate peptides that *bind* to the desired receptor. These peptides are then synthesized as *isolated peptides* and tested for receptor agonist activity. In particular, Wrighton notes that "[t]his discovery may form the basis for the design of *small molecule* mimetics of EPO" (see abstract; emphasis added) and that "[*s*]*mall molecule* EPO mimetics may have desirable pharmacological properties such as oral bioavailability or the ability to be delivered trans-dermally" (see page 463, emphasis added). The Examiner alleges that one of ordinary skill would be motivated to combine the references because it is well known that peptides generally have short serum half-lives (see page 7). This would be doing exactly the opposite of the teachings of Wrighton. The mimetics of Wrighton were developed for particular pharmacological properties, such as oral bioavailability; those properties would likely be destroyed by incorporating the peptides into immunoglobulins.

Applicants request clarification from the Examiner regarding rejections citing the Helms et al. reference. The Examiner rejects claims 1-3, 5-11, 18-19, 22-23, 36, 96, 99-101, and 104-126 under 35 U.S.C. 103(a) as being unpatentable over Barbas et al. (a) in view of Dower et al. and Barbas et al. (b) in view of Cwirla et al. and further in view of Wrighton et al. as evidenced by Helms. However, on page 7 the Examiner appears to be rejecting only the claims wherein at least one flanking sequence is included (in particular claims 2 and 3) using Helms et al. Claim 2 is

directed to a TPO receptor agonist comprising an immunoglobulin, wherein a portion of a CDR is replaced with a TPO mimetic and wherein at least one amino acid is covalently linked to at least one end of the mimetic.

The Examiner admits that Helms teaches that the introduction of novel sequences into CDRs can significantly diminish the stability of immunoglobulins. The Examiner alleges that Helms also discloses introducing flanking sequences covalently linked to the introduced CDR sequences. Nothing in the cited references or the general knowledge of one of ordinary skill would lead to a combination of Helms with any of the other cited references. The Barbas references are silent with regard to the stability of the immunoglobulins and in fact the immunoglobulins work for their intended purpose as antagonists. A person skilled in the art lacks any motivation to modify functional antagonists with flanking sequences from a reference that teaches the instability of its immunoglobulins. The Examiner has thus failed to demonstrate a finding that there was some teaching, suggestion, or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings.

Additionally, the Examiner has failed to demonstrate a finding that there was a reasonable expectation of success. The Examiner is required to articulate why a person skilled in the art would expect that a CDR replacement strategy that produces antagonists would result in EPO and TPO agonists.

The Examiner states that "the functions of the antibodies produced by the method of Barbas (a) are irrelevant" (see page 6). The functions of the antibodies of the prior art are in fact quite relevant in the examination of obviousness. The Examiner states further on page 7 that an ordinary skilled person would have had a reasonable expectation of success to increase the half-life of an agonist peptide by grafting into a human antibody framework CDRs. The relevant question, however, is whether an ordinary person would have had a reasonable expectation of success of producing functional agonists by grafting a peptide into a human antibody framework CDR. The Examiner provides no support that an ordinary person of skill would have expected to produce agonists using a method that previously produced only antagonists.

In fact, as evidenced by the Declaration of James D. Marks, submitted herewith, a person of ordinary skill at the time of the invention would not have had an expectation of success of

generating receptor agonists using a CDR replacement strategy that produces antagonists. As explained in the Declaration, agonists and antagonists mediate their functions by vastly different molecular mechanisms. An antagonist is only required to interfere with the binding of a receptor and its corresponding ligand, while an agonist must induce a conformational change in the receptor that transduces into an activation signal. The Declaration further explains that because of the specific conformation requirements required for activating a receptor, a person skilled in the art would not expect that the Cwirla and Wrighton peptides could be inserted into CDR regions and maintain their ability to 1) bind receptor, 2) dimerize receptor, and 3) activate receptor by providing the proper conformation of receptor assembly. Based on the knowledge of receptor activation and the teachings of Barbas, a skilled person would actually expect that insertion of peptides into a protein scaffold would likely interfere with the conformation of peptide-receptor binding and prevent receptor activation or could even result in formation of a receptor antagonist. Accordingly, the Examiner has clearly failed to demonstrate that one skilled in the art would have had a reasonable expectation of producing an agonist molecule comprising a peptide incorporated into a CDR of an immunoglobulin based on the teachings of the cited references.

Alternatively, the Examiner may be attempting to reject the claims as "obvious to try". The guidelines with regard to the "obvious to try" standard are set forth in Rationale E in the Examination Guidelines for Determining Obviousness under 35 U.S.C. 103:

(E) "Obvious to try" - choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success;

(1) a finding that at the time of the invention, there had been a recognized problem or need in the art, which may include a design need or market pressure to solve a problem;

(2) a finding that there had been a finite number of identified, predictable potential solutions to the recognized need or problem;

(3) a finding that one of ordinary skill in the art could have pursued the known potential solutions with a reasonable expectation of success; and

(4) whatever additional findings based on the *Graham* factual inquiries may be necessary, in view of the facts of the case under consideration, to explain a conclusion of obviousness.

The present claims relate to TPO and EPO receptor agonists comprising peptide mimetics inserted into CDR regions. At the time of the invention, the CDR replacement strategy of Barbas

was not one of the known predictable solutions of generating agonists with increased in vivo half-life. Applicants were the first to demonstrate that this strategy would work for generating agonists. Furthermore, as previously noted, the Examiner has failed to demonstrate that one of ordinary skill would have a reasonable expectation of success in generating agonists using a strategy shown to produce antagonists.

Claim Rejections Under 35 U.S.C. §112, first paragraph

Claims 1-3, 5-11, 18-19, 22-23, 36, 44, 85-87, 89, and 96-126 were rejected under 35 U.S.C. §112, first paragraph. The Examiner alleges that the specification does not enable an immunoglobulin or antigen fragment thereof comprising a CDR wherein a TPO mimetic replaces a single portion of said CDR. Applicants respectfully disagree.

The Examiner's attention is drawn to Example 7 in the specification which describes the construction of a heavy chain CDR2 library. CDR2 is *partially replaced* by the TPO mimetic peptide. The first 10 amino acids of CDR2 were replaced with 11 amino acids of TPO mimetic peptide and flanking sequence while 7 amino acids of CDR2 remain. The library was subsequently panned for binding to cMpl-R. The specification, therefore, provides a working example of an immunoglobulin wherein *a portion of a CDR* is replaced with a peptide mimetic.

Furthermore, Applicants respectfully disagree with the Examiner's reliance on the Rudikoff et al., Colman et al. and Ibragimova references. The Examiner points to the references to demonstrate that even minor changes within the CDR sequences are known to dramatically affect the binding function of an antibody. As Applicants have explained in our previous response (mailed April 19, 2007), the binding ability of the claimed immunoglobulin molecules does not depend on the precise three dimensional conformation of the CDR regions as is the case for conventional antibody-antigen interactions. The peptide mimetics are inserted into the CDRs only because these regions are solvent exposed. As opposed to a typical antibody wherein it is necessary for the six different CDRs to be in the proper conformation relative to each other for proper binding to the antibody target and where a change in the antibody sequence may disrupt the normal conformation, in the present case the immunoglobulin is acting as a carrier for a peptide and it is merely necessary for the peptide mimetic within the carrier to be exposed and to retain its activity, the remaining 5 CDRs are irrelevant. There is no need for six separate CDRs to bind a single target in the claimed